# CASE REPORTS

Refer to: Levine VD, Overturf GD, Mathies AW: Shigella dysenteriae type 1—Severe dysentery and sepsis with hematologic, hepatic and renal complications. West J Med 121:501-504, Dec 1974

## Shigella Dysenteriae Type 1

### Severe Dysentery and Sepsis with Hematologic, Hepatic and Renal Complications

VICTOR D. LEVINE, MD
GARY D. OVERTURF, MD
ALLEN W. MATHIES, PhD, MD
*Los Angeles*

BACILLARY DYSENTERY caused by Shigella dysenteriae* (Shiga dysentery) has occurred rarely in the United States, accounting for fewer than 1 percent of Shigella isolates up to 1969.[1] In early 1969, an epidemic strain of Shigella dysenteriae type 1 was responsible for a widespread epidemic in Guatemala and elsewhere in Central America.[2,3] In recent years, increasing numbers of cases (including two deaths) have been noted in Los Angeles.[4] Most domestic cases have been secondary to foreign importation, although some of the patients acquired the infection in the United States.

Since it was first recognized, in the latter part of the nineteenth century, Shiga dysentery has been associated with both clinical severity and high mortality.[5] The clinical dissimilarities from disease caused by other Shigella serotypes and its rare appearance in the United States emphasize the need for review of the illness caused by this organism. This report concerns several of the complications encountered in a severe case of Shiga dysentery.

*S. dysenteriae is the type species of the genus Shigella; subgroup A of shigellae which characteristically do not utilize manitol and are serologically distinct (serotypes 1-10) from members of the other subgroups (B,C,D).

From the Department of Pediatrics and Medicine, University of Southern California and the Communicable Disease Service, Los Angeles County/University of Southern California Medical Center, Los Angeles.

Submitted, revised, April 1, 1974.

Reprint requests to: G. D. Overturf, MD, LAC/USC Medical Center, General Laboratories Building 2-G-24, 1129 North State Street, Los Angeles, CA 90033.

### Report of a Case

A 16-year-old Mexican boy was admitted to the Communicable Disease Service of Los Angeles County-University of Southern California Medical Center (LAC/USC) on August 22, 1973, with complaint of diarrhea for four days. The patient had resided on a farm in Zamora, Mexico, and had come to visit the United States on August 17, 1973.

Four days before admission to hospital he noted onset of mild fever, crampy abdominal pain, and diarrhea consisting of 10 to 12 green, bloody, watery stools a day. The following day the patient no longer noted fever, but had nausea and profound vomiting. The day before admission (August 21), the patient was evaluated in the Communicable Disease admitting room and was found to have blood pressure of 118/75 mm of mercury, pulse rate of 76 and temperature of 37°C. The body weight was 53.0 kg. Other than increased bowel sounds and mild abdominal tenderness on palpation, the findings on physical examination were within normal limits. Laboratory data included hemoglobin of 18.8 grams per 100 ml, hematocrit 57 percent, leukocytes 8,000 per cu mm with 10 percent segmented and 48 percent banded forms, 26 percent lymphocytes, 13 percent monocytes, 1 percent basophils, 2 percent metamyelocytes and an occasional myelocyte. Platelets were normal in number. Blood sugar was 155 mg per 100 ml, blood urea nitrogen 14 mg per 100 ml, sodium 135 mEq, potassium 3.6 mEq, bicarbonate 31 mEq and chlorides 89 mEq per liter. On microscopic examination, the stool was watery and bloody with sheets of polymorphonuclear leukocytes. No ova or parasites were present. The evaluating physician's assessment noted the normal hydration and the absence of toxicity. The patient was sent home with instructions to take a clear liquid diet. The following day he returned with persistence of vomiting, an increase in bloody diarrhea, and dehydration.

On admission (August 22) the patient appeared only mildly toxic. The blood pressure was 110/70 mm of mercury, the pulse rate 100, respirations 36 per minute and temperature 37.2°C. The neck was supple, the chest clear, and findings on exami-

nation of the heart normal. The abdomen was not distended. Hyperactive bowel sounds were noted and there was mild diffuse tenderness and voluntary guarding. The liver and spleen were not enlarged. Examination of the skin showed no abnormalities except for decreased skin turgor. Body weight was 4.5 kg less than it had been the preceding day. There was no lymphadenopathy and no abnormality was noted on neurologic examination. Admission laboratory studies showed serum sodium of 126 mEq per liter and a BUN of 20 mg per 100 ml. Leukocytes numbered 12,400 per cu mm and there was still a pronounced shift to the left in cell differential. Platelets were present in adequate numbers. The hemoglobin content was 20.2 grams per 100 ml of blood and the hematocrit was 61 percent.

The impression on admission was of acute Shigella dysentery with decided fluid volume depletion, and therapy was begun accordingly. The patient was offered nothing by mouth and large amounts of fluids were given intravenously—14.0 liters over the first 72 hours. The patient continued, however, to have an output of 20 to 30 bloody stools a day totaling 4 to 6 liters, with little concurrent urine output. He remained afebrile, complaining of only mild to moderate crampy abdominal pain. During this time the blood pressure ranged from 110/70 to 90/60. Stool cultures obtained on August 21 grew Shigella dysenteriae type 1. A seven-day course of ampicillin, 150 mg per kg of body weight per day, intravenously, was begun on the second hospital day. Blood cultures obtained before therapy on August 23 also grew S. dysenteriae type 1. Susceptibility studies showed resistance to chloramphenicol, tetracycline, sulfonamide, and streptomycin, and susceptibility to ampicillin.

On the second hospital day, the patient's urinary output fell to less than 200 ml in 24 hours with a concurrent rise in the specific gravity to 1.030. Serum sodium fell to 116 mEq per liter. During the course of rehydration and with continued gastrointestinal hemorrhage the patient's hematocrit fell to 30 percent. The platelet count fell to 8,000 per cu mm by the third hospital day and fragmented red blood cells were seen on peripheral smear.

The Quick prothrombin time, partial thromboplastin time and thrombin time were all mildly prolonged. The result of a protamine test was positive, while fibrinogen showed a titer of 1:256 (>400 mg per 100 ml) and a factor VIII level was 223 percent. In addition, the patient was noted to be jaundiced, and liver function tests showed albumin of 1.9 grams, globulin 1.9 grams, and total bilirubin 7.0 mg per 100 ml (with 2.8 mg direct). Alkaline phosphatase was 3.3 B.L. units, SGOT 139 units, SGPT 37 units, and LDH 5,965 units. Abdominal distension developed concurrently with a gradual loss of bowel sounds and abdominal x-ray films were consistent with a paralytic ileus. By the third hospital day, ascites and peripheral edema became evident on physical examination.

Over the following week the serum creatinine rose from 1.2 to 7.1 mg and the BUN from 33 to 140 mg per 100 ml. Urinalysis during this time showed only minimal proteinuria and microscopic hematuria, without red cell casts. Urine output increased gradually during this time but progressive azotemia did not improve. On the fifth hospital day the leukocyte count reached 90,000 per cu mm, with numerous immature precursors seen on peripheral smear. On examination of bone marrow aspirate, there was evidence of pronounced toxic effect on all cell lines, including megakaryocytes which appeared slightly decreased in number. During this time the patient required 12 blood transfusions and 10 platelet packs due to gastrointestinal hemorrhage.

On the seventh hospital day (August 29) a Scribner shunt was placed in the patient's right arm and hemodialysis was carried out four times over the next eight days. Hepatic and renal dysfunction gradually resolved, with general improvement in his condition during dialysis. The bloody diarrhea which had persisted throughout the first two weeks in hospital gradually resolved during the third hospital week.

At the time of discharge on September 18, 1973, the patient was asymptomatic, with normal appetite, normal bowel movements, and no edema. Creatinine content was 1.5 mg per 100 ml, liver function tests were normal, and urinalysis was normal. The thrombocytopenia had resolved; however, the patient remained anemic; hemoglobin was 8.8 grams per 100 ml. On examination one week after discharge the patient was asymptomatic with normal renal and hepatic function and improving anemia.

## Discussion

Few isolations of Shigella dysenteriae type 1 had been recorded in the Western Hemisphere until the major epidemic of Shiga dysentery in Cen-

tral America in 1969.[3] An increase in the incidence of isolates of this organism in the United States has also been seen since 1969, mainly in travelers from Mexico and Central America.[6] However, several cases have been described in which no relevant travel history could be obtained, and spread within Los Angeles County was documented recently.[4] Assuming an incubation period of 5 to 7 days, in the present case the infection was most likely acquired in Mexico.

In the United States today, S. sonnei accounts for more than 80 percent of Shigella infections, with S. flexneri accounting for about 15 percent.[7] S. dysenteriae and S. boydii together have accounted for less than 1 percent. Shigella infection frequently presents as either a simple diarrheal illness or frank dysentery with high fever. However, the prominence of abdominal pain, nausea and vomiting, associated with minimal fever or toxicity early in the course distinguishes disease due to Shigella dysenteriae type 1 from that caused by other serotypes. Therefore, delays or confusion in diagnosis and treatment have been noted both in isolated cases and in epidemics of dysentery due to the Shiga bacillus.

Severe and prolonged gastrointestinal hemorrhage may be associated with extensive mucosal invasion and destruction.[8] In sporadic cases and during large epidemics, Shiga dysentery has been confused with ulcerative colitis and amebic dysentery. Several factors contribute to misdiagnosis. First, the Shiga bacillus has proved difficult to isolate with Salmonella-Shigella (SS) agar,[2] and often requires XLD, tergitol,[7] or MacConkey's agar for isolation. Second, this infection frequently coexists in regions endemic for Entamoeba histolytica, and the symptoms are mistaken for those of classical amebic dysentery. In the recent Central American epidemic, initial cases were thought to be secondary to Entamoeba histolytica, and trophozoites of E. histolytica were reported in the stools of some patients before the actual cause was established.[2] Finally, R-factor-mediated resistance to broad spectrum antibiotics commonly used in bacillary dysentery has led to the use of inappropriate antibiotic therapy. Virtually all isolates in Central America were resistant to chloramphenicol, tetracycline, and sulfathiazole, yet remained susceptible to ampicillin.[2]

During our patient's stay in hospital a pronounced granulocytic leukemoid reaction was noted. Leukocyte counts in blood have been variable in non-Shiga serotypes, with leukocytosis occurring more commonly than leukopenia. There is, however, a consistent and often pronounced shift to the left.[9] Our patient showed a dramatic fall in hematocrit, from 60 percent to 30 percent in 24 hours. The combination of intestinal bleeding, rehydration and hemolysis were all thought to play a role in this change. In addition, hematologic and hepatic dysfunction may have contributed to persistent lower intestinal hemorrhage. Thrombocytopenia is considered a rare complication.[9] The patient's thrombocytopenia was felt to be secondary to endotoxemia and sepsis. In addition, the morphologic abnormality of red blood cells associated with a positive protamine test[10] and prolonged prothrombin time and partial thromboplastin time suggested diffuse intravascular coagulation, and similarly this entity may have contributed to this patient's thrombocytopenia. Diffuse intravascular coagulation (DIC) was described in another recently reported case of S. dysenteriae type 1 disease in a five-year-old child.[11] In addition, a 14-month-old patient with a "hemolytic-uremic" syndrome has been described.[7]

Acute renal failure has been responsible for death in patients with acute shigellosis, although it is often difficult to separate renal failure due to infection from that due to profound dehydration. Both factors may have played a role in our patient's renal dysfunction, although acute tubular necrosis appeared to be a more likely explanation. In addition, diffuse intravascular coagulation has been associated with severe renal insufficiency.

Hepatic dysfunction has not been described frequently with shigellosis. In contrast to disease caused by the other Shigella serotypes, S. dysenteriae type 1 infection is frequently associated with bacteremia,[4] and alterations in renal and liver function and disturbances in coagulation are recognized complications of Gram-negative sepsis or endotoxemia. The frequent bacteremia and significant incidence of complications dictates systemic antibiotic therapy in infections due to S. dysenteriae, type 1. In contrast, antibiotic therapy in disease due to other Shigella serotypes has shown only modest benefit, at the expense of developing an alarmingly rapid increase in the incidence of resistant organisms.[14] Ampicillin is the drug of choice against the Shiga bacillus, particularly in view of R-factor-mediated resistance to chloramphenicol, streptomycin, sulfadiazine and tetracycline noted in the Central American epidemic.

Los Angeles County is currently an endemic

area for S. dysenteriae type 1. It is likely that more cases will appear in the United States, particularly in areas adjacent to Mexico. The insidious onset, the antibiotic resistance and the organism's potential for epidemic spread present a formidable problem. The association with episodes of prolonged intestinal hemorrhages, bacteremia, renal and hepatic dysfunction and coagulation disturbances further serves to emphasize the differentiation of disease produced by S. dysenteriae type 1 from that of other Shigella serotypes. The severity of the disease stresses the necessity of early recognition and initiation of appropriate aggressive antimicrobial and supportive therapy.

#### REFERENCES


1. Keller B, Gangarosa EI, Brachman PS: Shigellosis in the United States—Five-year review of nationwide surveillance, 1964-1968. Am J Epid 91:161-169, 1970

2. Mata LJ, Gangarosa EJ, Caceres A, et al: Epidemic Shiga bacillus dysentery in Central America—I. Etiologic investigations in Guatamala, 1969. J Inf Dis 122:170-180, 1970

3. Gangarosa EJ, Perera DR, Mata LJ, et al: Epidemic Shiga bacillus dysentery in Central America—II. Epidemiologic studies in 1969. J Inf Dis 122:181-190, 1970

4. Friedman CT, Western KA, Kamei I, et al: Shiga bacillus infection. JAMA 226:1559-1561, 1973

5. Block B, Gerguson WM: An outbreak of Shiga dysentery in Michigan, 1938. Am J Pub Health 30:43-52, 1940

6. Haltalin KC, Dickerson MS: Shiga dysentery—Texas. United States Department of Health, Education and Welfare, Center for Disease Control, Morbidity and Mortality Weekly Report, 21:221, 1973

7. United States Department of Health, Education and Welfare, National Communicable Disease Center, Atlanta, Georgia. Shigella Surveillance Report No. 34, 1973

8. Formal SB, Gemski P, Giannella RA, et al: Mechanisms of Shigella pathogenesis. Am J Clin Nutr 25:1427-1432, 1972

9. Barrett-Connor E, Connor JD: Extraintestinal manifestations of Shigellosis. Am J Gastroenterology 53:234-245, 1970

10. Kidder WF, Logan LJ, Rapaport SI, et al: The plasma protamine paracoagulation test. Am J Clin Path 58:675-686, 1972

11. Willis KC, Rosenblatt RM: Shiga bacillus dysentery complicated by bacteremia and disseminated intravascular coagulation. J Peds 83:90-93, 1973

12. Haltalin KC, Nelson JD, Ring R, et al: Double-blind treatment—Study of shigellosis comparing ampicillin sulfadiazine, and placebo. J Peds 70:970-981, 1967

13. Teng MJ, Martin DG, Cunningham JJ, et al: Clinical and bacteriological evaluation of antibiotic treatment in shigellosis. JAMA 214:1841-1844, 1970

14. Ross S, Controni G, Khan W: Resistance of shigellae to ampicillin and other antibiotics. JAMA 221:45-48, 1972


Refer to: Carey WD, Brotman M: Clindamycin colitis—An emerging problem. West J Med 121:504-507, Dec 1974

# Clindamycin Colitis —An Emerging Problem


WILLIAM D. CAREY, MD
*Rochester, Minnesota*

MARTIN BROTMAN, MD
*San Francisco, California*


ANTIBIOTIC THERAPY is a two-edged sword: efficacy on one edge, toxicity on the other. The benefits of a new agent are widely disseminated soon after its introduction; the toxicity, even if severe, often takes months and years to become known.

Clindamycin is a seven-deoxy, seven-chloro derivative of lincomycin, an antibiotic elaborated by an actinomycete, Streptomyces lincolnensis.[1] Gastrointestinal side effects of lincomycin therapy have been reported extensively; it has long been recognized that diarrhea is a regular accompaniment of lincomycin given by mouth.[1-4] These episodes have usually been self-limited once the offending agent was removed. More recently a pseudomembranous enterocolitis, at times fatal, has been described.[5-7] Most documented cases followed lincomycin by mouth, but a few followed parenteral administration.

Clindamycin is currently being used more and more widely as an agent for anaerobic and Gram-positive aerobic infections. Although the manufacturer's package insert and advertising include notice that penicillins remain the drugs of choice for many Gram-positive upper respiratory tract infections, clindamycin is clearly being advocated for control of many of these infections. However, this drug, like its parent, produces a diarrheal illness and recently has been incriminated with increasing frequency as a cause of pseudomembranous enterocolitis.[8-14] The incidence of diarrhea and pseudomembranous colitis are said to be distinctly lower with clindamycin than with lincomycin, although substantiation of this lower toxicity is lacking.

This paper describes the first reported fatal case of clindamycin colitis and reviews previous cases documented in the literature.

## Report of a Case

A 49-year-old Mexican woman was first admitted to the Pacific Medical Center in November, 1973, for hemodialysis following six months of weekly peritoneal dialysis elsewhere for idiopathic renal failure. Peritoneal dialysis had been uneventful except for episodic pleural effusion

From the Divisions of Nephrology and Gastroenterology, Presbyterian Hospital, San Francisco.

Submitted April 29, 1974.

Reprint requests to: M. Brotman, MD, 655 Sutter St., San Francisco, CA 94102.